Claim rejections under 35 U.S.C. 103

Claims 28-34 and 49-91 are rejected under 35 U.S.C. 103(a) as being obvious over PCT/FR95/00520 (published on Nov. 16, 1995 as WO95/30759, or the '759 publication).

Specifically, the Office Action asserts that the '759 publication teaches nucleic acid encoding a chimeric serum albumin (SA) with a useful heterologous peptide inserted anywhere therein (emphasis added), that the encoded chimeric SA polypeptide has increased *in vivo* stability, resulting in more stable peptides that lasts longer *in vivo* (which is allegedly useful for reducing frequency of painful injections). The Office Action also contends that the instant application is about increasing *in vivo* stability of a useful peptide by inserting it into SA, and that the specification does not teach unexpected results by inserting a useful peptide into the recited specific regions of SA. Thus, the Office Action concludes that the recited specific insertion region is just an "obvious variation" of the prior art teaching, and "it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to insert therapeutically desirable peptide biologically active peptides or polypeptides in order to increase *in vivo* half life t[o] reduce frequency of painful injection."

Pursuant to MPEP 706.02(j), three basic criteria have to be met before a *prima facie* case of obviousness rejection can be made: 1) the prior art references must teach or suggest all the claim limitations; 2) some motivation or suggestion, either found in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine or modify the references must be present; and 3) a reasonable expectation of success is required.

First of all, Applicants submit that, contrary to the Office Action's assertion, the '759 publication does not teach a skilled artisan that a heterologous peptide can be inserted anywhere into a serum albumin, especially not the regions recited in the claimed invention. Thus the claimed invention cannot be viewed as a mere obvious variation of the prior art disclosure.

Specifically, the '759 application states on page 6 (of the English translation) that "[t]he insertion of an active peptide into the peptide sequence of the albumin is conducted according to the invention in a manner so as to satisfy the following two conditions: A sufficient accessibility must be preserved at said active part, inserted into the core of the albumin, in order to keep intact its biological activity. Moreover, the structure of the albumin cannot undergo too much destabilization, which would, of course, be detrimental to the recombinant polypeptide called the

chimera." (emphasis added) Clearly, the '759 application limits the useful SA region for insertion to regions that satisfy both of these requirements (accessibility and limited destabilization), rather than "anywhere" as stated in the Office Action. Furthermore, the criteria set forth in the '759 application only define the insertion region by function, but not by structure. In other words, it only states the wished-for insertion regions with certain characteristics, as opposed to teaching a skilled artisan where these regions are located on SA. As discussed below, there may be many or just a few regions that fulfill both of these functional characteristics, and it is certainly not obvious to a skilled artisan as to where these regions are located based on the generalized speculation of the '759 application. Thus, the cited reference itself does not teach or suggest all the limitation of the claimed invention, it offers no motivation to combine with any (yet to be cited) references, and a skilled artisan would have no reasonable expectation of arriving at the specific regions recited in the present claims. Therefore, a *prima facie* case of obviousness cannot be established, and the insertion regions recited in the present claims cannot be regarded as obvious variations of the generic teachings of the '759 application.

The '759 application does disclose on page 7 (of the English translation) that "[t]he insertion sites are preferably localized in the regions of the albumin presumed to form exposed regions at the surface of the molecule, these regions preferentially being loops." However, based on the structure of SA described in the art (for example, see Figure 1 of the '759 application, and the preceding paragraphs before the recited paragraph on page 10), there are many potential loop structures or surface-exposed regions on each of the three domains of SA. The prior art does not teach that all of these regions may be suitable for insertion of heterologous peptides. Especially in view of the "limited destabilization" criterion set forth before, a skilled artisan would have no knowledge or ability to predict, without undue experimentation, which of these numerous surface exposed regions are stable enough to sustain an insertion event without destruction of the advantageous characteristics of SA or the inserted peptide. This suggestion constitutes nothing more than an invitation to further experimentation. Thus, the cited reference itself does not teach or suggest all the limitation of the claimed invention, it offers no motivation to combine with any (yet to be cited) references, and a skilled artisan would have no reasonable expectation of arriving at the specific regions recited in the present claims. Therefore, a *prima facie* case of obviousness cannot be established, and the insertion regions recited in the present claims cannot be regarded as obvious variations in view of this very general speculation.

The '759 application also suggests on page 7 a few specific insertion regions, including: three regions of the first domain (regions 5, 8, and 13), and one region of the third domain. However, none of these specific regions render the recited regions in the claimed invention obvious. For example, although region 5 of domain I and the domain III region (residues 419-430) are "loops," they are quite far away from either of the two claimed loop regions. There is no evidence of record to support the contention that these loops render the two claimed loops obvious. Region 8 is not a loop, but a "zone" between subdomains (see Figure 1). Region 13 is part of a helix (see page 7, 5th full paragraph, and Figure 1), which is also not a loop. Since there is no obvious inter-relationship, or common bonding characteristics between these disclosed insertion regions, it would not be readily apparent to a skilled artisan as to where other suitable insertion regions might be. Thus none of these specific disclosed embodiments renders the claimed invention obvious.

A second ground of Applicants' traverse is that the teachings of the '759 application, when viewed in light of the common knowledge in the art at the time of the filing, would not have convinced a skilled artisan that an inserted heterologous peptide would generally retain its biological property.

Specifically, the only example in the '759 application that purports to illustrate the preservation of the biological function of an inserted heterologous peptide is shown in Example 8 of the '759 application. In that Example, a four-amino-acid peptide (IEGR, SEQ ID NO: 21 of the '759 application), which is a cleavage recognition sequence for the protease factor Xa, is inserted into SA. It was shown that factor Xa can recognize and cleave this sequence at the non-physiological pH of 8.0 (the significance of which will be discussed below).

As a skilled artisan would appreciate, human serum albumin (HSA) is a protein of 66.5 kDa that is composed of three homologous domains, each of which displays specific structural and functional characteristics. HSA is known to undergo different pH-dependent structural transitions, the N-F and F-E transitions in the acid pH region and the N-B transition at slightly alkaline pH. Reviewed in Carter *et al.* (1994) Adv. Protein Chem. 45, 153-203 (cited by the instant Office Action below); and Peters, T., Jr. (1996) All About Albumin: Biochemistry, Genetics, and Medical Applications, Academic Press, Inc., New York.

E <-------> F <-------> N <-------> B <-------> A

pH of transition:	2.7		4.3	8	10
Name:	**E**xpanded	**F**ast	**N**ormal	**B**asic	**A**ged
% Helix:	35	45	55	48	48

Adapted from Carter *et al.*, *supra.*

The N-F transition involves the unfolding of domain III. The F form is characterized by a dramatic increase in viscosity, much lower solubility, and a significant loss in helical content. At pH values lower than 4, albumin undergoes another expansion with a loss of the intra-domain helices of domain I which is connected to helix of domain II, and that of helix of domain II connected to helix of domain III. This expanded form is known as the (E) form which has an increased intrinsic viscosity, and a rise in the hydrodynamic axial ratio from about 4 to 9. In the pH region of the N-B transition, domain I and domain II experience a tertiary structural isomerization.

As mentioned above, the only working examples of the '759 application are limited to the demonstration that a heterologous peptide inserted in an albumin protein can serve as a *substrate* for protease cleavage, under the non-physiological *in vitro* condition of pH 8.0 (which is about 10-times more basic as compared to the normal or physiological pH value of about 7. See page 30 of '759). At that pH, wild-type albumin undergoes the N-B transition. The B isomerization is understood as a structural fluctuation, a loosening of the molecule with loss of rigidity. Wilting *et al.* (1979) Biochim. Biophys. Acta 579:469-473; Bos *et al.* (1988) Biochem. Pharmacol. 37:3905-3909; and Bos *et al.* (1988) Biochim. Biophys. Acta 953: 37-47. Enzymes are generally able to tolerate, and in some cases are optimized for, substrate sequences in a protein that are present in a random coil configuration rather than part of a more rigid structural domain. Accordingly, under the circumstances, one skilled in the art would likely have been skeptical about the general applicability of chimeric albumin proteins even for other protein-protein interactions under discrete non-physiological aqueous conditions, let alone interactions at a cell surface.

Therefore, results presented in the instant application, conducted under physiological conditions in cultured cells, do more than merely reflect the achievement of an obvious prediction

that can be readily made based on the disclosure of the '759 application. They provide experimental confirmation of a new inventive concept set forth in the pending claims.

Pursuant to MPEP 2141, "[o]ffice policy is to follow *Graham v. John Deere Co.* in the consideration and determination of obviousness under 35 U.S.C. 103. As quoted above, the four factual inquires enunciated therein as a background for determining obviousness are as follows:

(A) Determining the scope and contents of the prior art;

(B) Ascertaining the differences between the prior art and the claims in issue;

(C) Resolving the level of ordinary skill in the pertinent art; and

(D) Evaluating evidence of secondary considerations."

In the instant case, several significant differences exist between the '759 application and the instant application. One is the specifically disclosed insertion regions in the instant application; another is the absence of relevant working examples carried out under physiological conditions in the '759 application. The prior art as a whole would not have taught one of ordinary skill in the art how to bridge these gaps between the disclosure of the '759 application and the claimed invention for the reasons stated above. Thus, none of the three requirements for establishing a *prima facie* case of obviousness has been satisfied. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. 103(a).

Double Patenting

Claims 28-34 and 49-91 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 28-33, and 54-104 of copending Application No. 09/768,183.

Applicants note that, pursuant to 37 CFR 1.130(b), a timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome a provisional rejection based on a commonly owned co-pending application. Applicants will submit a terminal disclaimer, if necessary, upon indication of allowable subject matter.

CONCLUSION

For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the pending rejections. Applicants believe that the claims are now in condition for allowance and early notification to this effect is earnestly solicited. Any questions arising from this submission may be directed to the undersigned at (617) 951-7000.

If there are any other fees due in connection with the filing of this submission, please charge the fees to our **Deposit Account No. 18-1945.** If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit account.

Respectfully Submitted,

Date: May 14, 2003

Yu Lu, Ph.D.
Reg. No. 50,306

Customer No: 28120
Docketing Specialist
Ropes & Gray LLP
One International Place
Boston, MA 02110
Phone: 617-951-7000
Fax: 617-951-7050